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(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ERICKSON, Magnus [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). JOSEFSSON, Lars [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

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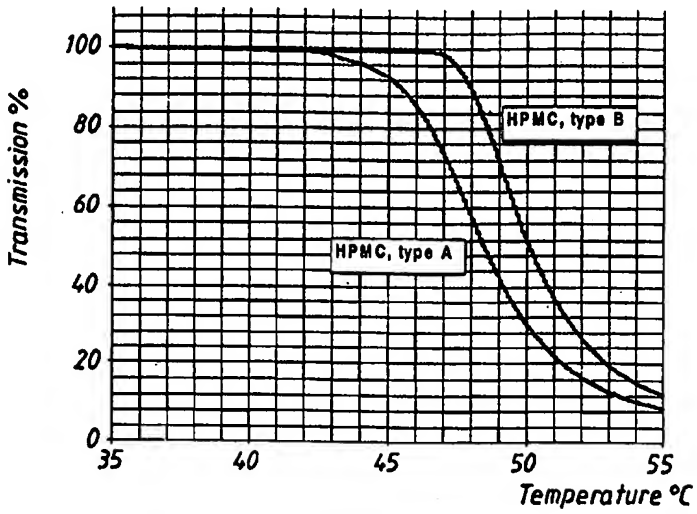

(57) Abstract

An enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole, wherein the formulation comprises a core material of the active ingredient and optionally an alkaline reacting compound, the active ingredient is in admixture with a pharmaceutically acceptable excipient, such as for instance a binding agent, and on said core material a separating layer and an enteric coating layer. A hydroxypropyl methylcellulose (HPMC) of low viscosity with a specific cloud point is used in the manufacture of pharmaceutical formulations. Furthermore, the application describes the processes for their preparation and the use of the claimed formulations in medicine.

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PHARMACEUTICAL FORMULATION OF OMEPRAZOLE

Field of the invention.

The present invention relates to an oral pharmaceutical formulation comprising the acid labile H^+, K^+-ATPase inhibitor omeprazole. The formulation is in the form of a multiple unit dosage form comprising enteric coating layered units of omeprazole. More specifically, the units comprise a core material of omeprazole and optionally an alkaline reacting substance, in admixture with one or more pharmaceutically acceptable excipients such as a binding, filling and/or disintegrating agent. Furthermore, each unit comprises a separating layer to separate the enteric coating layer from the core material. The separating layer and/or the optional binding agent consists of a specific quality of hydroxypropyl methylcellulose (HPMC), and optionally pharmaceutical excipients. More specifically, the HPMC quality has a specific cloud point.

Furthermore, the present invention refers to the use of a specific quality of HPMC in the manufacture of a pharmaceutical formulation comprising omeprazole, and the use of such a pharmaceutical formulation in medicine.

Background of the invention.

Omeprazole, an alkaline salt thereof, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole, all compounds hereinafter referred to as omeprazole, are used in the treatment of gastric acid related diseases. Omeprazole and pharmaceutically acceptable salts thereof are described in EP 5129, and some specific alkaline salts of omeprazole are described in EP 124 495 and WO95/01977. Certain salts of the single enantiomers of omeprazole and their preparation are described in WO94/27988.

Omeprazole is generally known to be useful for inhibiting gastric acid secretion in mammals and man by controlling gastric acid secretion at the final step of the acid secretory pathway. Thus, in a more general sense, it may be used for prevention and

treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcers and duodenal ulcers. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with non ulcer dyspepsia, in patients with symptomatic gastro-oesophageal reflux disease, and in patients with gastrinomas. It may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, it may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these, as well as in the treatment or prophylaxis of inflammatory conditions in mammals, including man.

Omeprazole is, however, susceptible to degradation or transformation in acidic and neutral media. The degradation is catalyzed by acidic compounds and is stabilized in mixtures with alkaline compounds. The stability of omeprazole is also affected by moisture, heat, organic solvents and to some degree by light.

With respect to the stability properties of omeprazole, it is obvious that an oral solid dosage form must be protected from contact with the acidic gastric juice and that omeprazole must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur.

A pharmaceutical oral dosage form of omeprazole is best protected from contact with acidic gastric juice by an enteric coating layer. In EP 247 983 such an enteric coated formulation of omeprazole is described. The formulation contains omeprazole in the form of a core unit containing omeprazole together with an alkaline salt or containing an alkaline salt of omeprazole optionally together with an alkaline salt, the core unit is layered with a separating layer and an enteric coating layer. In WO 96/01623 a multiple unit tableted dosage formulation of omeprazole is described.

The oral formulations described in EP 247 983 and the tablet formulations decribed in WO 96/01623 are enteric coating layered formulations which comprise or may comprise a separating layer to separate the acidic enteric coating material from omeprazole being an acid susceptible substance. HPMC of low viscosity may be used as a binding agent in the core material or as a layer separating the core material from the enteric coating layer in the described formulations. All ingredients, including HPMC qualities, used in a pharmaceutical preparations must fulfill strict criteria, such as for instance requirements defined in pharmacopoeial monographs.

The rate of release of omeprazole from a pharmaceutical dosage form can influence the total extent of absorption of omeprazole into the general circulation (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). Therefore the limits for rate of release of the omeprazole from the pharmaceutical formulation are stated in the marketing approval for the products.

It has now surprisingly been found that different batches of low viscosity HPMC, which fulfill all pharmacopoeial requirements, used as binder in the formation of omeprazole containing cores or as material for the separating layer of enteric coating layered formulations of omeprazole, may differ with respect to their ability of influensing the rate of release of omeprazole in simulated intestinal fluid, USP, *in vitro*. One parameter of interest in the release rate influensing ability of the HPMC is its water solublity.

The aqueous solubility of HPMC decreases with increasing temperature due to polymer phase separation. This is observed as a clouding of the polymer solution when the temperature is increased. Cloud point is the temperature at which this polymer phase separation occurs. Cloud point is determined by measuring the light transmission through the polymer solution. The light transmission of a specific system where the polymer is dissolved, that is a transparent polymer solution without clouding, is defined as light transmission 100 %. In this patent application cloud point is defined as the temperature where the light transmission of a specific system is 96% when a commercial instrument

from Mettler is used. For other cloud point systems and instruments another light transmisson may be specified for each system.

One problem which can be avoided by the new formulation and use of a specific quality of HPMC is that the amount of product discard can be reduced. From an economical aspect it is advantageous to specify and check the HPMC quality and keep the discard of produced pharmaceutical product low.

Outline of the invention.

It has now been found that a quality of HPMC with a cloud point of not less than 45.6°C determined as the temperature where the light transmission of a specified system is 96% measured by a Mettler FP90/FP 81C instrument is desirable in an enteric coating layered pharmaceutical formulation comprising omeprazole. Alternatively, when another instrument is used for determination, the cloud point may be specified as not less than 44.5°C when determined as the temperature where the light transmission is 95% measured by a spectrophotometer. The two different apparatuses used in cloud point determination are described more in detail in the experimental section, below. An upper limit for the cloud point is not critical and therefore there is no need to specify that.

The HPMC is used as a binding agent and/or as a constituent of a separating layer separating the core material from the enteric coating layer. The HPMC quality defined in the present patent application is desirable in fulfilling the criteria on rate of release of omeprazole and to be suitable for oral administration of omeprazole.

Detailed description of the drawings.

Figure 1 shows two graphs representing two different batches of low viscosity HPMC named Type A and Type B. The graphs show cloud point determinations for the two HPMC batches used as a constituent of the separating layer described in Example 1 below. With a separating layer comprising HPMC Type A the release of omeprazole was not

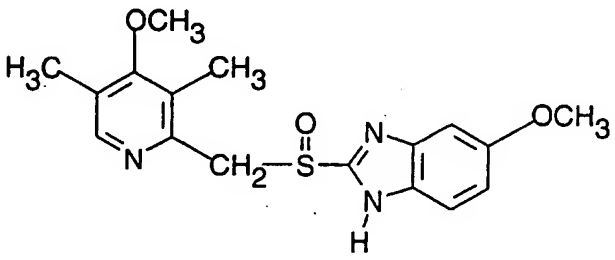
acceptable for a pharmaceutical product, and with the HPMC Type B none of the discussed problems with the rate of release of omeprazole in an oral formulation occured.
Figure 2 shows the same experiment as Figure 1 described in Example 2 below, but the cloud point determination has been performed in another equipment.

Figure 3 shows two graphs representing the release of omeprazole from core material with two different batches of low viscosity HPMC used as binding agent described in Example 3 below. The bars represent standard error of the mean. The release of omeprazole was followed by spectrophotometric determinations at 302 nm, and the graphs show that the release of omeprazole was delayed with a binding agent of the HPMC Type A compared with Type B.

Detailed description of the invention.

Core materials.

Omeprazole with formula Ia, is preferably formulated into an oral composition in the form of a pharmaceutically acceptable salt, such as an alkaline salt selected from the group of the Mg^{2+}, Ca^{2+}, Na^{+} and K^{+} salts, more preferably the Mg^{2+} salt. Omeprazole may also be used in the form of the (-)-enantiomer of omeprazole or an alkaline salt of the (-)-enantiomer of omeprazole.



(Ia)

The core material for the individually enteric coating layered pellets can be composed and formulated according to different principles, such as described in EP 247 983 and WO

96/01623 hereby incorporated by reference. For instance, omeprazole is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of omeprazole in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives, can be used.

Preferably, omeprazole, optionally after mixing with alkaline compounds, is mixed with suitable constituents including a binding agent and formulated into a core material. Said core materials may be produced by extrusion/spheronization, balling or compression utilizing different process equipments. The formulated core materials may have a size of less than approximately 2 mm. The manufactured core materials can be layered further with additional ingredients, optionally comprising active substance, and/or be used for further processing.

Alternatively, inert seeds layered with active substance (the active substance is optionally mixed with alkaline compounds) can be used as the core material for the further processing. The seeds, which are to be layered with the active substance, can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures.

Before the seeds are layered, for instance by using granulating or spray coating/layering equipment, omeprazole is mixed with a binding agent and optionally further components. Such further components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures.

The binders are for example celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, microcrystalline cellulose and carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. If hydroxypropyl methylcellulose is used as the binding agent, it is preferably a quality of HPMC with a cloud point of not less than 45.6°C determined as

the temperature where the light transmission of a specified system is 96% measured by a Mettler FP90/FP81C instrument, or alternatively the HPMC quality has a cloud point of not less than 44.5°C determined as the temperature where the light transmission is 95% measured by a spectrophotometer. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants, such as for instance sodium lauryl sulphate.

The active substance may also be mixed with an alkaline pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $Mg_6Al_2(OH)_{16}CO_3.4H_2O$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

Separating layer(s)

The core material containing omeprazole must, according to EP 247 983, be separated from the enteric coating polymer(s) containing free carboxyl groups, which may otherwise cause degradation/discolouration of omeprazole during the coating process or during storage.

According to the present invention, the separating layer comprises a specific quality of low viscosity HPMC, especially a HPMC with a viscosity of preferably less than 7.2 cps in 2% aqueous solution. This specific quality of HPMC should preferably have a cloud point of at least 45.6 °C determined by a Mettler instrument. The determination of cloud point may

be performed in another instrument and system as described in detail in the experimental section. The cloud point is determined in a mixed disodium hydrogenphosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5. The mixed solution used for the cloud point determination has a pH of 6.75 - 6.85. The concentration of HPMC in the mixed solution is 1.2% (w/w) for the Mettler instrument. For more detailed information on the composition of the mixed solution, see below in the experimental section.

Alternatively, the quality of HPMC is determined by a method which correlates with the above described methods, e.g. NIR spectrophotometry.

Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included in the separating layer(s).

Enteric coating layer(s)

One or more enteric coating layers are applied onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in a suitable organic solvent. As enteric coating layer polymers one or more, separately or in combination, of the following can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s). For environmental reasons, an aqueous coating process may be preferred. In such aqueous processes methacrylic acid copolymers are most preferred.

The enteric coating layers may contain pharmaceutically acceptable plasticizers to obtain desirable mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers. The amount of plasticizer is optimized for each enteric coating layer

formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s). Additives such as dispersants, colorants, pigments, polymers e.g. poly(ethylacrylate, methylmethacrylate), anti-tacking and anti-foaming agents may also be included in the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acidic susceptible active substance.

To protect the acidic susceptible active substance, the enteric coating layer(s) preferably constitute(s) a thickness of at least approximately 10 µm. The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

The pellets or units covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the layering process.

Final dosage form.

The prepared pellets may be filled in hard gelatine capsules or compressed with suitable tablet excipients into a tableted multiple unit formulation. Final dosage forms include effervescent tablets, and also combinations of omeprazole with other active ingredients, such as for instance antibacterial substances, NSAID(s), motility agents or antacids.

Experimental section.

Examples 1and 2: Test of omeprazole pellets layered with two different types of low viscosity HPMC used as a constituent of the separation layer.

Omeprazole pellets prepared according to the description in EP 247 983 (correspond to pellets from a Losec® capsule) were tested with respect to rate of release of omeprazole.

According to the marketing approval for the Losec® capsule formulation at least 75 % of the omeprazole in a dose must be released within 30 minutes in a buffer solution.

The pellets were pre-exposed to simulated gastric fluid USP (without enzyme) at 37°C for 2 hours. Thereafter the drug release in buffer solution pH 6.8 at 30 minutes was determined by liquid chromatography. The buffer solution pH 6.8 was a mixture of 100.0 parts of simulated gastric fluid USP (without enzyme) and 80.0 parts of 0.235 M disodium hydrogen phosphate solution, pH should be between 6.75 and 6.85. The simulated gastric fluid USP (without enzyme) was prepared by dissolving 2.0 g NaCl and 7.0 ml conc. HCl and add water to 1000 ml. The 0.235 M disodium hydrogen phosphate solution was prepared by dissolving 41.8 g $Na_2HPO_4.2H_2O$ and add water to 1000 ml.

The composition of the tested omeprazole pellets was as follows.

I. Core material with the following composition was prepared.

Core material			
Omeprazole		10.4	kg
Mannitol		74.3	kg
Hydroxypropylcellulose		3.1	kg
Microcrystalline cellulose		2.1	kg
Lactose anhydrous		4.2	kg
Disodium hydrogen phosphate		0.41	kg
Sodium lauryl sulphate		0.26	kg
Water	approx	19	kg

II. The prepared core material was coating layered with a separating layer consisting of HPMC, type A or type B. The separating layers with the following composition were applied in the stated amount.

Separating layer

Uncoated pellets from above	120	kg
Hydroxypropyl methylcellulose 6cps	4.8	kg
Water	96	kg

III. The prepared core material with a separating layer was further coating layered with an enteric coating of the following composition.

Enteric coating layer

Prepared pellets from above	120	kg
Methacrylic acid copolyme	27.3	kg
Polyethylene glycol	2.7	kg
Water	150	kg

Omeprazole pellets prepared with separating layer of two different qualities of HPMC 6cps, i.e type A and type B, were tested according to the description above. The pellets were prepared from the same batch of omeprazole, and with the same enteric coating material. The release of omeprazole within 30 minutes in a buffer solution was determined.

Cloud point determination was performed with two different apparatuses. In Example 1 a commercial equipment from Mettlers was used and in Example 2 a spectrophotometer equipped with a heating coil and stirring function was used. The experimental conditions and used apparatuses are described below.

Pellets containing HPMC	Cloud point [°C] Ex. 1 (n=2)	Ex. 2 (n=1)	Release of omeprazole from enteric coated pellets [%]
Type A	44.4	42.5	69 (60-84)
Type B	47.5	47.2	93 (93-94)

The results from cloud point determination for the two HPMC qualities are shown in Figures 1 and 2. As can be seen in the table above with the HPMC Type A the release of omeprazole was not acceptable for a pharmaceutical product, but with the HPMC Type B none of the discussed problems with the rate of release of omeprazole in an oral formulation occured.

Results from a number of experiments with different batches of HPMC indicate that HPMC with a cloud point of at least 45.6°C is desirable in fulfilling the regulatory requirements on rate of release of omeprazole, when the cloud point determination is performed in a commercial Mettler instrument.

Cloud point determination. of the HPMC types in the Mettler instrument was conducted in the following way. The cloud point of the HPMC types was determined in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5. The mixed solution had a pH of 6.75 - 6.85. The concentration of HPMC 6 cps in the mixed solution was 1.2% (w/w). It is essential for the specificity of the cloud point determination that this system is used in the choosen instrument. The Mettler instrument comprises the following parts: Mettler FP90 Central processor, FP81C Measuring unit and ME-18572 boiling point tubes. A temperature range of 35.0 to 55.0°C was used and a heating rate of 1.0°C/min. The results are shown in Figure 1.

Alternatively, a spectrophotometer equipped with a heating coil and a stirring function was used for the cloud point determination. The concentration of HPMC in the buffer solution was 1.0% (w/w). The equipment measured corresponding temperature and transmission values. Depending on the character of the HPMC to be analysed, the temperature interval of interest varies. A temperature range of 35 - 50°C was relevant for most samples. A delay time of 5 minutes at each new temperature setting was used before transmission reading. The results are shown in Figure 2.

Example 3: Test of different types of low viscosity HPMC used as binding agent in the preparation of core material for pellets.

I. Core material with the following composition was prepared by spray layering in a fluidized bed. An aqueous suspension of omeprazole magnesium salt and HPMC was sprayed onto sugar spheres. Two batches of pellets were prepared using HPMC type A and type B, respectively. The same batch of omeprazole-Mg was used for both experiments.

Sugar spheres	200	g
Omeprazole-Mg	200	g
Hydroxypropyl methylcellulose 6 cps	30	g
Water	920	g

The prepared pellets were tested with respect to rate of release of omeprazole in buffer solution pH 6.8 with identical composition as in Example 1, 37 °C, paddle speed 100 rpm. The release of omeprazole was followed by spectrophotometric determination (302 nm) and the results are presented in Figure 3. The graphs show that the release of omeprazole was delayed for the HPMC Type A compared with Type B. Since the pellets were not coated with a separating layer and an enteric coating layer they were not pre-exposed to simulated gastric fluid.

Claims.

1. An enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole, wherein the formulation comprises a core material of the active ingredient and optionally an alkaline reacting compound, the active ingredient is in admixture with one or more pharmaceutical acceptable excipients such as a binding, filling and/or a disintegrating agent, and on said core material a separating layer and an enteric coating layer, characterized in that a hydroxypropyl methylcellulose (HPMC) of low viscosity with a cloud point of at least 45.6°C determined as the temperature where the light transmission of the system is 96%, is used as a binding agent and/or a consituent of the separating layer, and wherein the cloud point is determined in the following way: the HPMC is dissolved in a concentration of 1.2% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75-6.85, or that the HPMC used as a binding agent and/or a constituent of the separating layer has a low viscosity with a cloud point of at least 44.5°C determined as the temperature where the light transmission of a system is 95%, and wherein the cloud point is determined in the following way: the HPMC of low viscosity is dissolved in a concentration of 1% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

2. A formulation according to claim 1, wherein the HPMC of low viscosity is used as a constituent of a separating layer.

3. A formulation according to claim 2, wherein the enteric coating layer comprises a methacrylic acid copolymer.

4. A formulation according to claim 1, wherein the HPMC of low viscosity is used as a binding agent.

5. A formulation according to claim 1, wherein the HPMC of low viscosity has a viscosity of less than 7.2 cps in 2% aqueous solution.

6. A formulation according to claim 1, wherein the active ingredient is omeprazole.

7. A formulation according to claim 1, wherein the active ingredient is a magnesium salt of omeprazole.

8. A formulation according to claim 1, wherein the active ingredient is a magnesium salt of the (-)-enantiomer of omeprazole.

9. Use of a quality of hydroxypropyl methylcellulose (HPMC) of low viscosity with a cloud point of at least 45.6°C at which the light transmission of a system is 96%, in the manufacture of an enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole, wherein the formulation comprises a core material of the active ingredient and optionally an alkaline reacting compound, the active ingredient is in admixture with one or more pharmaceutically acceptable excipients such as a binding, filling and/or disintegrating agent and on said core material a separating layer and an enteric coating layer, characterized in that the separating layer comprises a HPMC of low viscosity with a cloud point as defined above and the cloud point is determined in the following way: the HPMC is dissolved in a concentration of 1.2% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

10. Use of a quality of hydroxypropyl methylcellulose (HPMC) of low viscosity with a cloud point of at least 44.5°C at which the light transmission of a system is 95%, in the

manufacture of an enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole, wherein the formulation comprises a core material of the active ingredient and optionally an alkaline reacting compound, the active ingredient is in admixture with one or more pharmaceutically acceptable excipients such as a binding, filling and/or disintegrating agent and on said core material a separating layer and an enteric coating layer, characterized in that the separating layer comprises a HPMC of low viscosity with a cloud point as defined above and the cloud point is determined in the following way: the HPMC is dissolved in a concentration of 1% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

11. Use of a quality of hydroxypropyl methylcellulose(HPMC) of low viscosity with a cloud point of at least 45.6°C at which the light transmission of a system is 96%, in the manufacture of an enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole, wherein the formulation comprises a core material of the active ingredient and optionally an alkaline reacting compound, in admixture with at least a binding agent, and on said core material at least an enteric coating layer, characterized in that the binding agent is a HPMC of low viscosity with a cloud point as defined above and the cloud point is determined in the following way: the HPMC is dissolved in a concentration of 1.2% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

12. Use of a quality of hydroxypropyl methylcellulose(HPMC) of low viscosity with a cloud point of at least 44.5°C at which the light transmission of a system is 95%, in the manufacture of an enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of

omeprazole, wherein the formulation comprises a core material of the active ingredient and optionally an alkaline reacting compound, in admixture with at least a binding agent, and on said core material at least an enteric coating layer, characterized in that the binding agent is a HPMC of low viscosity with a cloud point as defined above and the cloud point is determined in the following way: the HPMC is dissolved in a concentration of 1% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

13. Use according to any of claim 9-11 or 12, wherein the HPMC has a viscosity of less than 7.2 cps in 2% aqueous solution.

14. A process for the manufacture of an enteric coated oral pharmaceutical formulation defined in claim 1, wherein the active substance optionally mixed with an alkaline reacting compound and/or a binding agent, is formulated into a core material and on said core material a separating layer is coating layered, and thereafter an enteric coating layer is applied, characterized in that the separating layer comprises a hydroxypropyl methylcellulose HPMC of low viscosity with a cloud point of at least 45.6°C at which the light transmission of a system is 96%, and the cloud point is determined in the following way: the HPMC is dissolved in a concentration of 1.2% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

15. A process for the manufacture of an enteric coated oral pharmaceutical formulation defined in claim 1, wherein the active substance optionally mixed with an alkaline reacting compound and/or a binding agent, is formulated into a core material and on said core material a separating layer is coating layered, and thereafter an enteric coating layer is applied, characterized in that the separating layer comprises a hydroxypropyl methylcellulose HPMC of low viscosity with a cloud point of at least 44.5°C at which the light transmission of a system is 95%, and the cloud point is determined in the following way: the HPMC is dissolved in a concentration of 1% (w/w) in a mixed solution of

phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

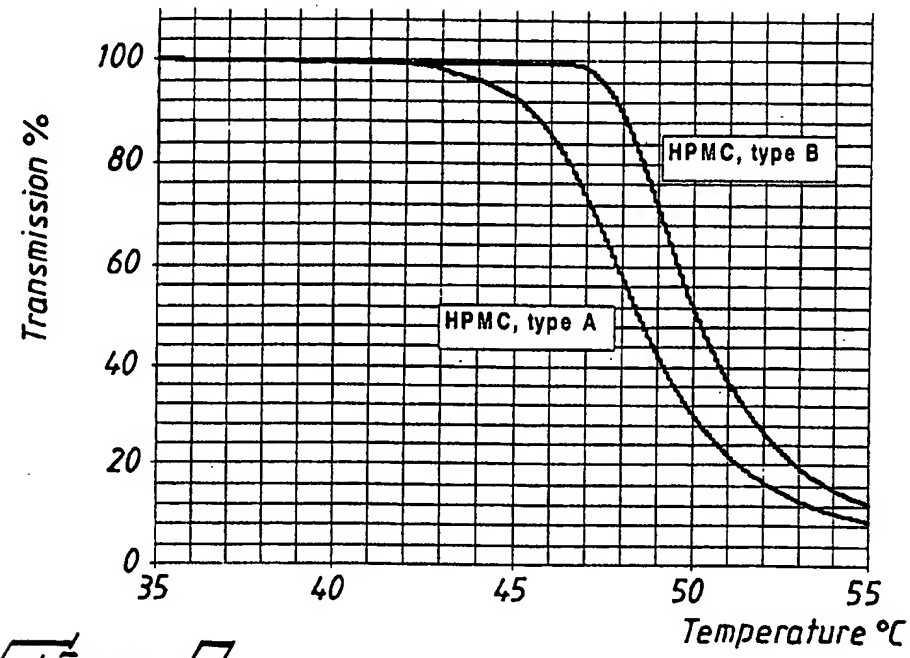
16. A process for the manufacture of an enteric coated oral pharmaceutical formulation defined in claim 1, wherein the active substance optionally mixed with an alkaline reacting compound, is mixed with a binding agent and formulated into a core material, on said core material at least one enteric coating layer is applied, characterized in that the binding agent comprises a hydroxypropyl methylcellulose HPMC of low viscosity with a cloud point of at least 45.6°C at which the light transmission of a system is 96%, and the cloud point is determined in the following way: the HPMC is dissolved in a concentration of 1.2% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

17. A process for the manufacture of an enteric coated oral pharmaceutical formulation defined in claim 1, wherein the active substance optionally mixed with an alkaline reacting compound, is mixed with a binding agent and formulated into a core material, on said core material at least one enteric coating layer is applied, characterized in that the binding agent comprises a hydroxypropyl methylcellulose HPMC of low viscosity with a cloud point of at least 44.5°C at which the light transmission of a system is 95%, and the cloud point is determined in the following way: the HPMC is dissolved in a concentration of 1% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

18. Use of a pharmaceutical formulation as defined in any of claims 1 - 8 for the manufacture of a medicament for in the treatment of gastrointerstinal diseases.

19. A method for the treatment of gastrointestinal diseases in mammals including man by administrating to a host in need thereof a therapeutically effective dosage form defined in any of claims 1 - 8.

Fig. 1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80
60
40
20
0
35
40
45
50
55
Temperature °C
HPMC, type B
HPMC, type A

Fig. 2

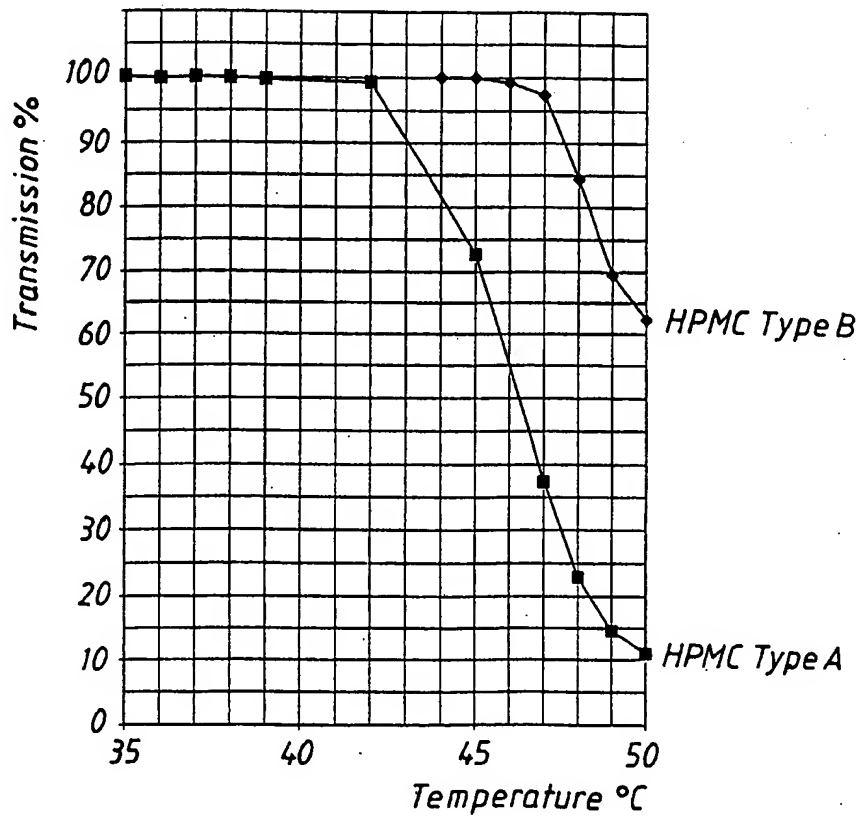
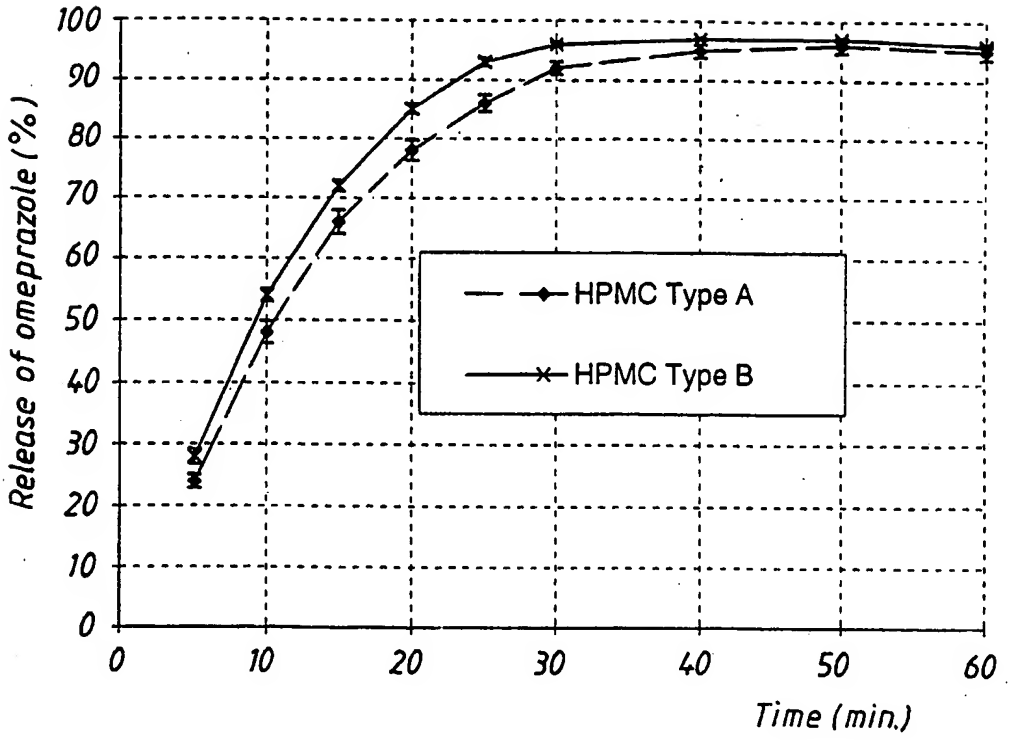

Transmission %
100
90
80
70
60
50
40
30
20
10
0
35
40
45
50
Temperature °C
HPMC Type B
HPMC Type A

Fig. 3


Release of omeprazole (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
Time (min.)
HPMC Type A
HPMC Type B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00922

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/28, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, EMBASE, WPI, CLAIMS, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87) --	1-19
A	WO 9601623 A1 (ASTRA AKTIEBOLAG), 25 January 1996 (25.01.96) --	1-19
A	US 5372998 A (HIROYASU KOKUBO ET AL), 13 December 1994 (13.12.94), claims --	1-19

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 Sept 1998	11 -09- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00922

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claim 19 is directed to a method of treatment of the human or animal body by a therapy method practised on the human or animal body /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compositions.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.
PCT/SE 98/00922

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INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.
PCT/SE 98/00922

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